

REMARKS

Applicant has amended claim 1 to delete the recitation of piperidine and, therefore, to encompass only compounds wherein Ring A is a tetrahydroquinoline or tetrahydroisoquinoline. Support for this amendment may be found throughout the specification as originally filed. In particular, see pages 14-15, disclosing each of the Ring A compounds as separate embodiments.

Applicant has amended claim 1 to clarify that "F₂" in the definition of R³ indicates two fluorine atoms being bound to formula I. To aid this clarification, applicant has amended formula I to have a radical R^{3'} in addition to radical R³. Applicant has also amended claim 1 to clarify the attachment of various radicals to formula I.

Applicant has amended claim 2 and added claims 20-22 and 26-27 to present original claim 2's subject matter in separate claims. Support for this amendment may be found throughout the specification as originally filed (e.g., in original claim 2).

Applicant has amended claim 3 to delete the Ar definition (for not further limiting Ar - see claim 1).

Applicant has amended claim 7 to recite the structures of the compounds being claimed rather than referring to Table 1 that disclosed those structures. Applicant has also amended claim 7 to be an independent claim. Support for this amendment

may be found throughout the specification as originally filed (e.g., Table 1 at page 16, line 15 through the end of page 22).

Applicant has amended method claim 8 to refer to each of the compound claims 1-3, 5-7 or 18-42. Applicant has therefore deleted the now redundant recitation of formula I in claim 8 and cancelled claims 9-11.

Applicant has amended claim 12 to correct a typographical error and for clarity.

Applicant has amended claim 14 to be an independent claim and to refer to pending compound claims 1-3, 5-7, and 18-42. Applicant has amended claim 15 to depend from 14. Applicant has amended claim 14 and claim 15 to delete the recitation of "derivative" and for grammatical clarity.

Applicant has amended claim 17 to refer to pending compound claims 1-3, 5-7, and 18-42.

Applicant has added claims 18-42 directed to further embodiments of this invention. Claims 20-22 and 26-27 are addressed above; the other claims are addressed below.

Claim 18 and claim 19 are directed to Ring A embodiments. Support for this amendment may be found throughout the specification as originally filed (see e.g., page 15, lines 1-10, disclosing preferred A rings).

Claims 23-25 are directed to compounds having preferred R^3 groups. Support for the amendment may be found throughout the specification as originally filed (see e.g., page 16, lines 7-8).

Independent claims 28-31 are directed to compounds wherein ring A is a piperidine ring. Support for these claims may be found throughout the specification as originally filed (see, e.g., page 9, line 24 to page 10, line 9; page 10, lines 12-28; page 14, line 20; and page 15, line 22 to page 16, line 11).

Claims 29 and 30 recite the definition for electronegative leaving group disclosed in the specification as originally filed at page 11, line 29 to page 12, line 7 (rather than the phrase "electronegative leaving group"). Applicant has amended the definition of electronegative leaving group to distinguish the R group therein (now R') from the R group of the broadest R¹ embodiment.

Claims 31-42 recite preferred embodiments of this invention. Support for the amendment may be found throughout the specification as originally filed (see, e.g., page 16, lines 3-11 and the claims as originally filed).

None of these amendments adds new matter.

The Office Action

The Declaration

The Examiner contends that the Declaration is defective and has required submission of a new Declaration. Applicant is amending the inventorship in this application and will submit a

new Declaration concurrent with submission of the inventorship petition.

The Objections

Claim 12 stands objected to for reciting "or" unnecessarily at page 86, line 27. Applicant has amended claim 12 to delete this "or" thus obviating this objection.

Claims 14 and 15 stand objected to under 37 C.F.R § 1.75(c) "as being of improper dependent form for failing to further limit the subject matter of a previous claim." The Examiner contends that claims 14 and 15 are broader than claim 12 because they recite the term "derivative" and encompass *ex vivo* and *in vitro* methods as well as *in vivo* methods. Applicant has deleted the term derivative in response to the Examiner's 112, second paragraph rejections thus obviating this aspect of the objections. Applicant has also amended claims 14 to be independent and claim 15 to depend from claim 24 thus obviating the remaining objections.

For all of the above reasons, applicant requests that the Examiner withdraw the above objections.

The Rejections

35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 7-9, and 11-17 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to "particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicant traverses each of the Examiner's specific contentions below.

1. The Examiner contends that the definition of R^1 in claim 1 and claim 8 is unclear because the structure of " CHN_2 " is unclear. " CHN_2 " depicts a diazo group. Diazo groups may be

depicted also as: $CH \overset{\ominus}{-} N \overset{\oplus}{\equiv} N$. Diazo groups are well known to those of ordinary skill in the art (see, Concise Encyclopedia Chemistry, Mary Eagleson, ed., pp. 315-316, (1993), attached herewith as Exhibit 1). It is also well known that diazo groups would be depicted typically as monovalent.

Thus, the recitation of " CHN_2 " would be clear to skilled practitioners and does not render claims 1 and 8 unclear. Nevertheless, to more specifically recite this group, applicant has amended claim 1 to insert a hyphen immediately before " CHN_2 " (i.e., " $-CHN_2$ "). For consistency, applicant has also amended claim 1 to recite hyphens in the other variables in the R^1 definition.

The Examiner contends that the definition of R^3 in claim 1 and claim 8 is unclear because R^3 requires a monovalent group, but nonetheless recites F_2 as a possible definition.

Applicant has amended to clarify that each fluorine atom in F_2 would be bound to formula I. To aid this clarification, applicant has added a radical $R^{3'}$ to formula I. The definition of $R^{3'}$ is hydrogen in all instances except where R^3 is a fluorine atom. This definition is consistent with the specification as originally filed and thus adds no new matter.

Dependent claims 2 and 9 stand rejected for repeating the same definition of Ar as is recited in each claim's parent claim (i.e., claim 1 and claim 8, respectively). Applicant has amended claim 2 and claim 9 to no longer recite a definition of Ar thus obviating this rejection.

The Examiner contends that claim 7 and claim 11 are indefinite for incorporating by reference structures from a Table. Applicant has amended claim 7 to recite the compounds from the Table and cancelled claim 11. These amendments obviate the Examiner's rejections.

The Examiner contends that claim 12 is indefinite for reciting "various forms of liver disease including." The Examiner has suggested that applicant amend claim 12 to delete this phrase and recite instead "liver disease." Applicant has amended claim 12 as suggested by the Examiner thus obviating this rejection (by deleting "various forms of" and "including").

The Examiner contends that claims 14 and 15 are indefinite for reciting the term "derivative." Applicant has amended claims 14 and 15 to delete the term "derivative" thus obviating this rejection.

35 U.S.C. § 102

Claims 1, 2, 8, 9, 12, 16, and 17 stand rejected under 35 U.S.C. § 102 as being anticipated by Ohmoto et al., U.S. 6,136,834 ("Ohmoto et al."). The Examiner contends that Ohmoto et al. examples 18(23), 18(24), 19(21), and 19(22) fall within the scope of applicant's formula I in claims 1, 2, 8, 9, 12, 16, and 17. Applicant traverses.

Applicant has amended formula I to delete "piperidine" in the definition of Ring A. As amended, Ring A is only tetrahydroquinoline or tetrahydroisoquinoline. The Ohmoto et al. examples cited by the Examiner had piperidine rings at the position corresponding to Ring A. Furthermore, Ohmoto et al. disclose no compounds having tetrahydroquinoline or tetrahydroisoquinoline rings corresponding to Ring A. Thus, Ohmoto et al. fall outside the scope of formula I recited in amended claim 1 and claims 2, 8, 9, 12, 16, and 17 referring either directly or indirectly thereto.

For all of the above reasons, applicant requests that the Examiner withdraw these § 102 rejections.

35 U.S.C. § 103

Claims 13-15 stand rejected under 35 U.S.C. § 103 as being obvious over Ohmoto et al. in view of Hagmann et al. (U.S. Patent 5,866,545) and Baust et al. (U.S. Patent 6,045,990). The Examiner contends that Ohmoto et al. teach compounds falling within the scope of formula I, but "do not teach using their ICE inhibitors to treat complications associated with coronary artery bypass grafts, or to preserve cells, organs to be transplanted, or blood products." The Examiner further contends that Hagmann et al. "disclose the use of ICE inhibitors to treat graft rejection and graft-versus-host disease" and that Baust et al. "disclose the use of caspase protease inhibitors to treat animal or human organs, tissues or cells for hypothermic storage, e.g., prior to transplantation." The Examiner concludes, therefore, that "[i]t would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made" to use the Ohmoto et al. ICE inhibitors to treat the diseases of Hagmann et al. and Baust et al. Applicant traverses.

As addressed more fully herein, applicant's amended claims do not encompass any Ohmoto et al. compound. The Examiner's 103 rejections are based on Ohmoto et al. compounds falling within applicant's claims and are therefore obviated by the amendments presented herein. Accordingly, applicant requests that the Examiner withdraw these § 103 rejections.

08/07/2003 16:18 FAX

The Allowable Subject Matter

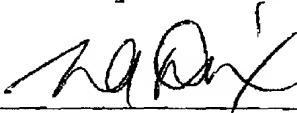
Claim 3-6 and 10 stand "objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form." The Examiner has also stated that claim 7 and claim 11 would be allowable if "rewritten to overcome the rejections(s) under 35 U.S.C. 112, second paragraph ... and to include all of the limitations of the base claim and any intervening claims."

Applicant respectfully suggests that the amended claims are allowable over Ohmoto et al. The Examiner has based his provisional allowability on Ohmoto et al.'s teaching. Specifically, the Examiner has noted that Ohmoto et al. "do not teach or suggest the R^1 group required by instant claims 3-7, 10, and 11" i.e., the CH_2F group. Applicant's amended claims 2, 3, 5, 6, 7, 21, 26, 35, 38, 40, and 42 are directed to compound wherein R^1 is CH_2F and should therefore be allowable. Amended claims 18-20, 22-25, 27-34, 36, 37, 39, and 41 also fall outside the scope of Ohmoto et al., and applicant therefore respectfully suggests that these claims should also be allowable. As these compound claims are allowable, applicant also respectfully suggests that claims 8, 12-16, and 17 directed to methods and pharmaceutical compositions involving these compounds should also be allowable.

Conclusion

In view of the above, applicant requests that the Examiner enter the above amendments, consider the foregoing remarks, and allow the pending claims to issue.

Respectfully submitted,



Lisa A. Dixon (Reg. No. 40,995)
Attorney for Applicant

VERTEX PHARMACEUTICALS INCORPORATED
130 Waverly Street
Cambridge, Massachusetts 02139
Telephone: (617)444-6396
Facsimile: (617)444-6483